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Intermolecular 1,5-Dipolar Cycloaddition Reaction of Tungsten-Containing Vinylazomethine Ylides Leading to Seven-Membered Heterocycles

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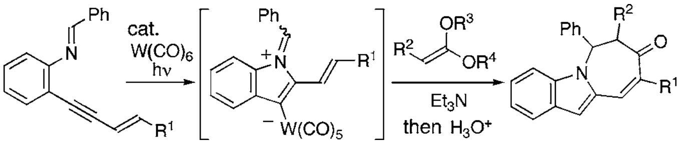
ABSTRACT



Intermolecular 1,5-dipolar cycloaddition reaction of tungsten-containing vinylazomethine ylide, generated from *o*-(alk-3-en-1-ynyl)phenylbenzaldimines and tungsten carbonyl complex, with ketene acetals proceeds efficiently to give azepino[1,2-*a*]indole derivatives in good yield. Formation of [5 + 2] or [3 + 2] cycloadducts can be controlled by an appropriate choice of dipolarophile.

Nitrogen-containing seven-membered rings often constitute the basic structure of a variety of biologically active compounds,[1] and development of useful methods for the preparation of these molecules is highly desirable. In contrast to the well-established 1,3-dipolar cycloaddition reaction of azomethine ylides for the construction of nitrogen-containing five-membered rings,[2] the [5 + 2] cycloaddition reaction of the corresponding vinylogous species, vinylazomethine ylides, is scarcely realized[3,4] because they easily undergo 1,5-electrocyclization[5] to give five-membered products or react preferentially as a 1,3-dipole to give [3 + 2] cycloadducts with a vinyl substituent.[6] In this paper, we describe a useful method for the preparation of various tricyclic indoles

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(1) For reviews on azepine derivatives, see: (a) O'Hagan, D. *Nat. Prod. Rep*. **1997**, 637. (b) Evans, P. A.; Holmes, B. *Tetrahedron* **1991**, *47*, 9131. (c) Bremner, J. B. In *Progress in Heterocyclic Chemistry*; Gribble, G. W., Joule, J. A., Eds.: Elsevier: Oxford, UK, 2003; Vol. 15, p 385. For some natural products having an azepino[1,2-*a*]indole skeleton, see: (d) Angenot, L.; Diberg, O.; Dupont, L. *Tetrahedron Lett.* **1975**, *16*, 1357. (e) Chbani, M.; Païs, M. *J. Nat. Prod.* **1993**, *56*, 99. (f) Massiot, G.; Thépenier, P.; Jacquier, M. J.; Delaude, C.; Le Men-Olivier, L.; Verpoorte, R. *Tetrahedron Lett.* **1985**, *26*, 2441.

(2) For reviews on 1,3-dipolar cycloaddition of azomethine ylides, see: (a) Padwa, A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: Oxford, U.K., 1991; vol. 4, p 1069. (b) Harwood, L. M.; Vickers, R. J. In *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry Toward Heterocycles and Natural Products*; Padwa, A., Pearson, W. H., Eds.; Wiley-Interscience: Hoboken, 2003; p 169. (c) Coldham, I.; Hufton, R. *Chem. Rev.* **2005**, *105*, 2765.

(3) Only a few specific examples for [5 + 2] cycloaddition of 1,5-dipoles in general have been reported; see: (a) Rothenberger, O. S.; Taylor, R. T.; Dalrymple, D. L.; Moore, J. A. *J. Org. Chem.* **1972**, *37*, 2640. (b) Cameron, A. F.; Freer, A. A. *Acta Crystallogr.* **1974**, *B30*, 2696. (c) Saito, T.; Nagashima, M.; Karakasa, T.; Motoki, S. *J. Chem. Soc., Chem. Commun.* **1992**, 411. (d) Barluenga, J.; Tomás, M.; Bieger, K.; García-Granda, S.; Santiago-García, R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 896. (e) Barluenga, J.; Tomás, M.; Bieger, K.; García-Granda, S.; Santiago-García, R. *J. Organomet. Chem.* **1997**, *529*, 233.

(4) (a) Wender et al. recently reported the first transition-metal-catalyzed hetero-[5 + 2] cycloaddition; see; Wender, P. A.; Pedersen, T. M.; Scanio, M. J. C. *J. Am. Chem. Soc.* **2002**, *124*, 15154. (b) For a pioneering work on the metal-catalyzed [5 + 2] cycloaddition, see: Wender, P. A.; Takahashi, H.; Witulski, B. *J. Am. Chem. Soc.* **1995**, *117*, 4720. For other examples of metal-mediated [5 + 2] cycloaddition, see: (c) Zhang, Y.; Liebeskind, L. S. *J. Am. Chem. Soc.* **2006**, *128*, 465. (d) Lee, S. I.; Park, S. Y.; Park, J. H.; Jung, I. G.; Choi, S. Y.; Chung, Y. K.; Lee, B. Y. *J. Org. Chem.* **2006**, *71*, 91. (e) Wegner, H. A.; de Meijere, A.; Wender, P. A. *J. Am. Chem. Soc.* **2005**, *127*, 6530. (f) Ashfeld, B. L.; Martin, S. F. *Org. Lett.* **2005**, *7*, 4535. (g) Trost, B. M.; Shen, H. C.; Horne, D. B.; Toste, F. D.; Steinmetz, B. G.; Koradin, C. *Chem.—Eur. J.* **2005**, *11*, 2577. (h) Tanino, K.; Kondo, F.; Shimizu, T.; Miyashita, M. *Org. Lett.* **2002**, *4*, 2217. (i) Tanino, K.; Shimizu, T.; Miyama, M.; Kuwajima, I. *J. Am. Chem. Soc.* **2000**, *122*, 6116. (j) Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 3909. (k) Malinakova, H. C.; Liebeskind, L. S. *Org. Lett.* **2000**, *2*, 4083. (l) Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *122*, 2379. (m) Yueh, T.-C.; Lush, S.-F.; Lee, G.-H.; Peng, S.-M.; Liu, R.-S. *Organometallics* **1996**, *15*, 5669.

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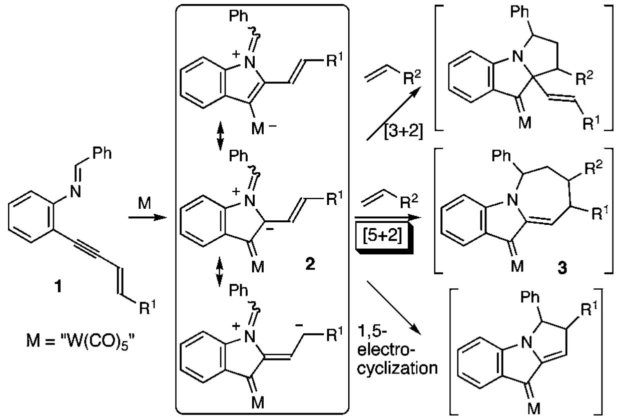
containing a seven-membered ring utilizing a novel [5 + 2] cycloaddition reaction of tungsten-containing vinyl-azomethine ylide species.[7]

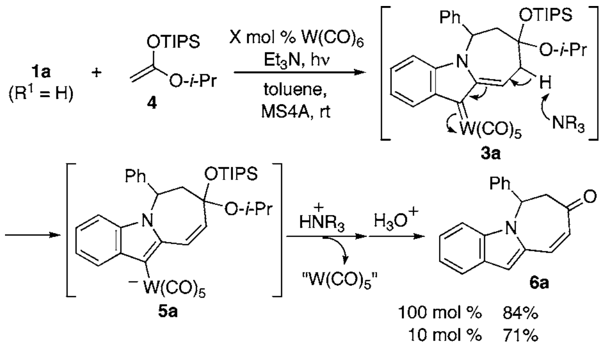
Our basic strategy is as follows: treatment of *o*-(alk-3-en-1-ynyl)phenylbenzaldimine **1** with $W(CO)_5(L)$ gives the tungsten-containing vinylazomethine ylide **2** through nucleophilic attack of the imino nitrogen onto the $W(CO)_5$-activated alkyne moiety. This ylide has the ability to react with alkenes as a 1,3-dipole or a 1,5-dipole in a [3 + 2] or a [5 + 2] manner giving tricyclic indoles containing a 5-membered ring or a 7-membered ring, respectively (Scheme 1). Additionally, it might also give a tricyclic indole through 1,5-electrocyclization. We expected the mode of cycloaddition to be controlled by the appropriate choice of the reactants.

Scheme 1



After several attempts, it was found that when *o*-(but-3-en-1-ynyl)phenylbenzaldimine **1a** was treated with an equimolar amount of $W(CO)_6$ and 2 molar equiv of ketene isopropyl triisopropylsilyl acetal **4** in the presence of MS4A and Et_3N under photoirradiation in toluene at ambient temperature, followed by mild acid treatment of the crude product, the desired azepino[1,2-*a*]indole derivative **6a** was eventually obtained in 84% yield (Scheme 2). The product **6a** was formed by deprotonation of the α,β-unsaturated carbene complex intermediate **3a** produced by the expected [5 + 2] cycloaddition of the tungsten-containing vinylazomethine ylide **2a** ($R^1 = H$) and the ketene silyl acetal **4**, followed by protonation of the generated dienyltungsten anion **5a**. Furthermore, the reaction proceeded smoothly only slightly lowering the yield even with a catalytic amount (10 mol %) of $W(CO)_6$. It should be noted that, in the present reaction, 1,5-electrocyclization of the tungsten-containing vinylazomethine ylide intermediate **2** is inhibited probably due to its rigid planar structure fused with the indole nucleus, in which the two reacting sites are located far from each other.

Scheme 2. Initial Attempt for the [5 + 2] Cycloaddition Reaction



As the novel [5 + 2] cycloaddition reaction of tungsten-containing vinylazomethine ylide was found to proceed as expected, we next examined the generality of this reaction (Table 1). As a dipolarophile, ketene acetals also gave good results. For example, diethyl ketene acetal or diisopropyl ketene acetal reacted smoothly with *o*-(but-3-en-1-ynyl)-phenylbenzaldimine **1a** to give the same product **6a** in good yield after mild acid hydrolysis (entries 1 and 2). Furthermore, methyl- or methoxy-substituted ketene silyl acetal also reacted smoothly under catalytic conditions to give the corresponding substituted tricyclic indoles as a mixture of diastereomers in good yield (entries 3 and 5). More interestingly, when sterically less demanding cyclic ketene acetal **7** was employed, [3 + 2] cycloaddition followed by 1,2-vinyl migration[7a,b,g] proceeded to give a dioxolane-protected derivative of tricyclic indole **8a** ($R^1 = R^2 = H$) containing a five-membered ring selectively in good yield (entry 6). Thus, [5 + 2] cycloadditions are favored over [3 + 2] cycloadditions with bulkier dipolarophiles, probably due to too strong steric repulsions between reacting centers in the latter case. Concerning the generality of the imine counterpart, the reaction of pent-3-en-1-ynyl derivative **1b** ($R^1 = Me$) proceeded smoothly to give the desired [5 + 2] cycloaddition product **6b** ($R^1 = Me$, $R^2 = H$) in good yield by using ketene diisopropyl acetal as dipolarophile (entries 7 and 8). Here again, use of a less bulky diethyl ketene acetal gave the [3 + 2] cycloadduct **8b** selectively in good yield (entry 9). The terminal methyl substituent of **1b** increases the steric repulsion in the [5 + 2] cycloaddition pathway, allowing the [3 + 2] cycloaddition reaction to proceed even

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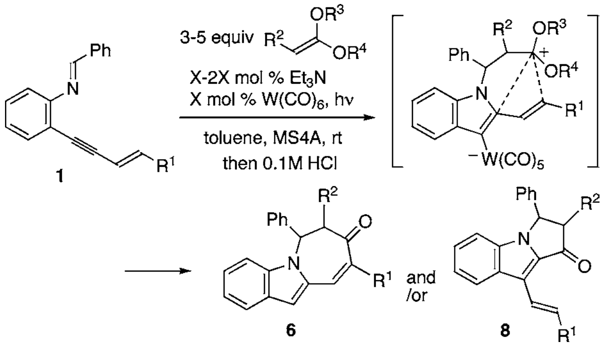
(5) For reviews on 1,5-electrocyclization of 1,5-dipoles, see; (a) Taylor, E. C.; Turchi, I. J. *Chem. Rev.* **1979**, *79*, 181. (b) Huisgen, R. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 947. Some recent examples for 1,5-electrocyclization of vinylogous azomethine ylides, see: (c) Nyerges, M.; Pintér, Á.; Virányi, A.; Blaskó, G.; Tőke, L. *Tetrahedron* **2005**, *61*, 8199. (d) Voznyi, I. V.; Novikov, M. S.; Khlebnikov, A. F. *Synlett* **2005**, 1006. (e) Wu, P.-L.; Chung, T.-H.; Chou, Y. *J. Org. Chem.* **2001**, *66*, 6585.

(6) (a) Epperson, M. T.; Gin, D. Y. *Angew. Chem., Int. Ed.* **2002**, *41*, 1778. (b) De Boeck, B.; Viehe, H. G. *Tetrahedron* **1998**, *54*, 513. (c) Coldham, I.; Collis, A. J.; Mould, R. J.; Robinson, D. E. *Synthesis* **1995**, 1147. (d) Bourhis, M.; Vercauteren, J. *Tetrahedron Lett.* **1994**, *35*, 1981. (e) Chen, S.-F.; Ullrich, J. W.; Mariano, P. S. *J. Am. Chem. Soc.* **1983**, *105*, 6160.

(7) For generation and reaction of tungsten-containing azomethine ylides, see: (a) Kusama, H.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2002**, *124*, 11592. (b) Takaya, J.; Kusama, H.; Iwasawa, N. *Chem. Lett.* **2004**, *33*, 16. For generation and reaction of tungsten-containing carbonyl ylides, see: (c) Kusama, H.; Funami, H.; Shido, M.; Hara, Y.; Takaya, J.; Iwasawa, N. *J. Am. Chem. Soc.* **2005**, *127*, 2709. (d) Iwasawa, N.; Shido, M.; Kusama, H. *J. Am. Chem. Soc.* **2001**, *123*, 5814. See also: (e) Shin, S.; Gupta, A. K.; Rhim, C. Y.; Oh, C. H. *Chem. Commun.* **2005**, 4429. (f) Kim, N.; Kim, Y.; Park, W.; Sung, D.; Gupta, A. K.; Oh, C. H. *Org. Lett.* **2005**, *7*, 5289. For generation of platinum-containing carbonyl ylides, see: (g) Kusama, H.; Funami, H.; Takaya, J.; Iwasawa, N. *Org. Lett.* **2004**, *6*, 605.

Table 1. Generality of Intermolecular [5 + 2] Cycloaddition

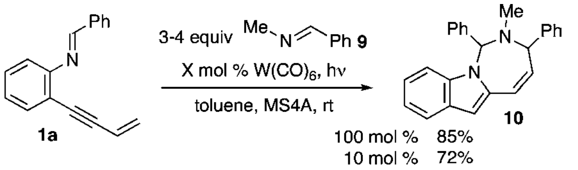


entry	R^1	R^2	R^3	R^4	$W(CO)_6$ (mol %)	yield (%) 6	yield (%) 8
1	H	H	*i*-Pr	*i*-Pr	10	62	
2	H	H	Et	Et	100	79	<15
3[a]	H	Me	TIPS	Et	10	72	
4[a]	H	OMe	TIPS	Et	100	71	
5[a]					10	61	
6	H	H	$-CH_2CH_2-$ **7**		100		76[b]
7	Me	H	*i*-Pr	*i*-Pr	100	64	28
8[c]					20	60	24
9	Me	H	Et	Et	100	6	76

[a] To neat Et_3N and dipolarophile was slowly added an imine solution for 6−7.5 h. The product was obtained as a mixture of diastereomers (ca. 1:1). [b] The product was isolated as a ketal without acidic workup. [c] The reaction was performed at 10 °C.

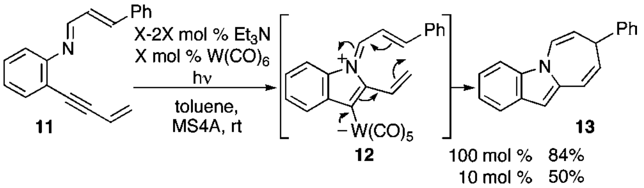
with diethyl ketene acetal. Thus, either [5 + 2] or [3 + 2] cycloadduct could be obtained selectively by appropriate choice of the dipolarophile.

Furthermore, imines were found to be good dipolarophiles in this reaction. For example, reaction of **1a** with imine **9** gave the diazepine derivative **10** as a mixture of diastereomers in good yield. This reaction proceeded even with a catalytic amount of $W(CO)_6$.



Finally, the reaction of cinnamaldimine derivative **11** was examined. In this case, another interesting 7-membered ring formation was found to proceed smoothly.

Treatment of imine **11** with a stoichiometric amount of $W(CO)_6$ under photoirradiation gave another azepino[1,2-*a*]indole derivative **13** in 84% yield. The reaction could proceed even with a catalytic amount of $W(CO)_6$, although the yield was lowered to 50%. This product was produced by 1,7-electrocyclization[8] of the tungsten-containing 1,5-dipole **12**, followed by Et_3N-induced deprotonation−protonation of the carbene complex intermediate.



In conclusion, we have developed a novel method for the construction of tricyclic indoles containing a seven-membered ring utilizing [5 + 2] cycloaddition reaction of tungsten-containing vinylazomethine ylides. This reaction is a very rare example of 1,5-dipolar cycloaddition and affords a useful method for the preparation of various synthetically valuable compounds.

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Supporting Information Available: Preparative methods and spectral and analytical data of compounds **1**, **6**, **8**, **10**, **11**, and **13**. This material is available free of charge via the Internet at http://pubs.acs.org.

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[8] For reviews on 1,7-electrocyclization, see: (a) Zecchi, G. *Synthesis* **1991**, 181. (b) Groundwater, P. W.; Nyerges, M. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press: New York, 1999; Vol. 73, p 97. For some recent examples for 1,7-electrocyclization, see: (c) Knobloch, K.; Koch, J.; Keller, M.; Eberbach, W. *Eur. J. Org. Chem.* **2005**, 2715. (d) Nyerges, M.; Pintér, Á.; Virányi, A.; Bitter, I.; Tőke, L. *Tetrahedron Lett.* **2005**, *46*, 377. (e) Reisser, M.; Maas, G. *J. Org. Chem.* **2004**, *69*, 4913 and references therein.